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# Hepatitis B Virus Reactivation and Management of Patients Undergoing Immunosuppression

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## Abstract

Hepatitis B reactivation (HBR) occurs in patients with inactive or resolved hepatitis B virus (HBV) infection, in whom the host immune response is overtaken by the replicative drive of the virus. While HBR may be clinically silent, there is abrupt reappearance or rise of HBV DNA in the serum (usually > 2 log) with or without a flare of alanine aminotransferase (ALT) activities. HBR commonly occurs in the setting of B-cell depleting agents and corticosteroids although cytotoxic chemotherapeutic and other immunosuppressant and immunomodulant agents may precipitate it. The risk of HBR may be determined by host characteristics, viral factors, and the type of medical therapy. For an optimal outcome, screening for patients at risk of HBR is critical. For patients identified to be at risk, strategic utilization of antiviral prophylaxis has been shown to improve outcomes.

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## Keywords

Hepatitis B • Reactivation • Immunosuppression

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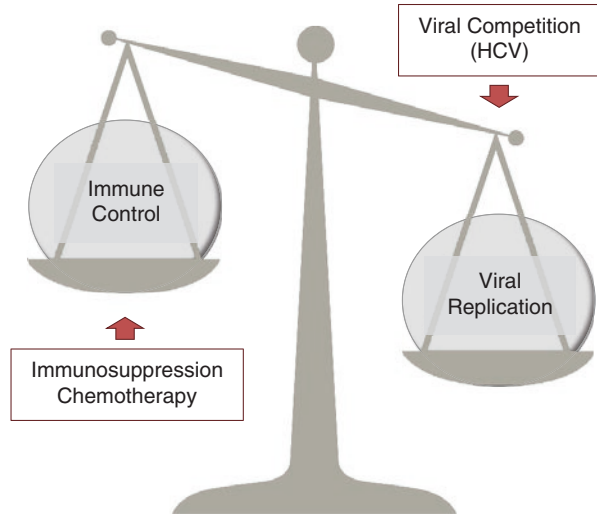
## 1 Introduction

Hepatitis B reactivation (HBR) is characterized by an abrupt reappearance or rise of hepatitis B virus (HBV) DNA in the serum of a patient with previously inactive or apparently resolved HBV infection (Lok et al. 1991). Compared to their baseline status of minimal or inactive disease activity, patients experiencing HBR may end up with recrudescence or flare of hepatitis activity. The most severe end of the spectrum may be symptomatic acute hepatitis, which may progress to fulminant liver failure.

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**Fig. 16.1** The occurrence of HBR depends on the balance between the replicative drive of the virus and the immune response from the host



In the background of HBR is the balance between the replicative drive of the virus and the immune response from the host (Fig. 16.1) (Lok et al. 1991; Yeo et al. 2004a). In patients with inactive HBV infection, viral replication is inhibited as a result of the control by the host immune system. HBR occurs when this balance is perturbed by an environmental agent such as an immunosuppressive or cancer therapeutic compound which lifts the immune control allowing HBV replication to resume (Hoofnagle 2009; Keam et al. 2011). More recently, there may be another mechanism to HBR when there is a coexistent hepatotropic virus such as hepatitis C virus (HCV). Successful eradication of HCV with recently available direct-acting antiviral agents has been associated with HBR.

Although HBR is often temporary and clinically silent, it may cause a symptomatic flare of hepatitis. While the flare in and of itself may evolve into a serious condition incurring morbidity and even mortality, another major clinical consequence of HBR is the need for interruption of immunosuppressive or chemotherapy. Moreover, in patients who are not suspected to have HBV infection, HBR may be a source of confusion and misdiagnosis, leading to a delay in appropriate clinical management. Hence, preventing HBR protects the patient from experiencing potentially dangerous flares and from failing to achieve the intended goals of the immunosuppressive therapy.

In this chapter, we will review the current literature on HBR and discuss its epidemiology, risk factors and mechanisms, manifestations and diagnosis, and clinical management in terms of prevention and therapy. We will also discuss challenges and future research direction and devote a section on the recent topic of HBR in the setting of HBV-HCV dual infection.

## 2 Mechanisms of HBR

HBV genome is able to persist in the liver for long periods of time, even when HBsAg is cleared in the serum. In patients in whom HBV infection is inactive, viral replication is suppressed by immune control of HBV infection, which is mediated through HBV-specific cytotoxic T cells (Rehermann et al. 1996; Zhang et al. 2012), while B cells also play a role in antigen presentation and viral clearance (Chang and Lewin 2007). Administration of an immunosuppressive drug to chronic HBV patients may potentially allow the virus to escape the immune control, leading to increased HBV replication and a marked increase in expression of HBV transcription intermediaries and products within hepatocytes (Kean et al. 2011).

### 2.1 Corticosteroids

Corticosteroids have a number of ways to promote HBV replication. The HBV genome has a glucocorticoid-responsive element which enhances replication of the virus (Tur-Kaspa et al. 1986; Calabrese et al. 2006; Tur-Kaspa et al. 1988). In a recent prospective study, half of the study patients had increased HBV DNA levels within 2 weeks of starting a corticosteroid-containing chemotherapy regimen. This occurred well before the development of neutropenia, suggesting a direct stimulatory effect of corticosteroids on HBV DNA transcription (Cheng et al. 2003). Indirectly, corticosteroids have a number of immunosuppressive effects including inhibition of cytotoxic T-cell function (Tur-Kaspa et al. 1988). The risk of HBR among those treated with corticosteroid varies by the dosages, duration of treatment, and HBV serologic status of the host.

### 2.2 B-Cell-Depleting Agents

Rituximab and ofatumumab are the two licensed monoclonal antibodies against CD20 of B cells in the USA, which possess potent immunosuppressive effects. They are used to treat hematologic malignancies and, less commonly, severe autoimmune diseases such as rheumatoid arthritis and vasculitis. While the mechanism of rituximab-/ofatumumab-associated HBV reactivation is not completely understood, the putative mechanisms are that depletion of B cells and the resulting disruption of antigen presentation impair CD8+ cytotoxic T cell's ability to kill HBV-infected hepatocytes. Anti-CD20 antibodies reduce the number of CD4 memory T cells, increase Th1/Th2 and Tc1/Tc2 ratios, and upregulate Fas ligand on Th1 and Th2 cells, further impairing the host immune control against the virus (Evens et al. 2011; Misumi and Whitmire 2014; Tsutsumi et al. 2015). B-cell depletion may lead to loss of anti-HBs (Pei et al. 2012).

## 2.3 Cytotoxic Chemotherapeutic and Immunosuppressant Agents

Cytotoxic cancer chemotherapeutic agents disrupt cell cycles, leading to DNA destruction. Subsequent activation of chemotherapy-induced DNA repair mechanisms results in a cascade of responses including upregulation of promyelocytic leukemia protein (PML) and PML nuclear body (PML-NB), which have been linked with increased HBV pregenomic transcription, HBV-core expression, and HBV DNA replication (Chung and Tsai 2009). Traditional immunosuppressants such as methotrexate, azathioprine, and 6-mercaptopurine also disrupt DNA synthesis. However, these are apparently not as detrimental from the standpoint of HBR as other chemotherapeutic agents (Calabrese et al. 2006; Droz et al. 2013; Flowers et al. 1990).

## 2.4 Biological Immunomodulants

HBV-specific cytotoxic T cells inhibit hepatocellular HBV gene expression and replication through a noncytotoxic mechanism, which is mediated in part by TNF- $\alpha$  and interferon- $\alpha$  (Kasahara et al. 2003; Tzeng et al. 2014). Inhibition of TNF- $\alpha$  activity may lead to enhanced viral replication (Carroll and Forgione 2010). Currently, there are three commonly used TNF- $\alpha$  inhibitors, etanercept, infliximab, and adalimumab, all of which have been implicated in HBR.

Cytokine or integrin inhibitors have been introduced in practice only in the past few years, and reported experience of HBR related to these agents is limited. Abatacept blocks costimulation of T lymphocytes (Herrero-Beaumont et al. 2012). Imatinib and other tyrosine kinase inhibitors can inhibit T-cell activation and proliferation (Seggewiss et al. 2005; Dietz et al. 2004). Ustekinumab is a human monoclonal antibody that is directed to interleukin-12 and interleukin-23 (Cingoz 2009). Natalizumab and vedolizumab are recently developed inhibitors to the cell adhesion molecule  $\alpha$ 4 integrin found on lymphocytes (Hutchinson 2007; Rezaie 2014). While empirical data are lacking, the direct effects of these agents on T-cell immunity raise concerns that the risk of HBR may be significant (Perrillo et al. 2015).

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## 3 Incidence of HBR

The accurate incidence of HBR among patients with immunosuppressive therapy is poorly defined for a number of reasons. First, the settings in which HBR occurs are heterogeneous depending upon host characteristics, baseline HBV status, types of immunosuppressive therapy, and the underlying disease that requires the immunosuppressive therapy. Second, most studies are conducted in retrospective fashion and would be enriched with patients with severe HBR requiring medical attention. Finally, the criteria to diagnose HBR are not uniformly defined, creating further

heterogeneity in study results. With these caveats, we summarize data regarding the incidence of HBR according to the clinical scenario.

### 3.1 Patients Undergoing Cancer Chemotherapy

HBR was initially described in cancer patients undergoing chemotherapy. Today, the most common scenario for HBR to occur in cancer therapy is patients with hematological malignancies receiving anti-CD20 antibodies. The incidence of HBR is much lower with cytotoxic chemotherapy for solid tumors, with breast cancer being one of the most frequently tumors associated with HBR. The incidence of HBR in HBsAg+ patients being treated for cancer has been reported to be 14–72%, whereas it is much lower (<3%) among patients who are HBsAg–/anti-HBc+ (Lok et al. 1991; Kim et al. 2007; Kumagai et al. 1997; Yeo et al. 2000a, b; 2003; 2004b; Kusumoto et al. 2009; Vento et al. 2002). In patients receiving a regimen including anti-CD20 antibodies, the incidence of HBR may be as high as 60% in those with HBsAg+ (Abramson and Chung 2014; Mendez-Navarro et al. 2011; Mozessohn et al. 2015). Even in patients who are HBsAg–/anti-HBc+, HBR may be seen in 8–42%.

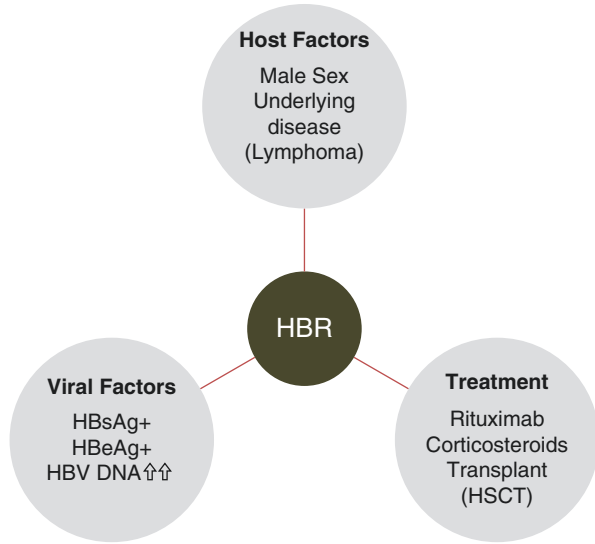
In addition to systemic chemotherapy, HBR may also occur in patients undergoing regional therapy such as transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC). Although the incidence of HBR in those settings has not been accurately defined, it may be as high as 34% (Jang et al. 2004).

### 3.2 Patients Undergoing Organ/Cell Transplantation

#### 3.2.1 Hematopoietic Stem Cell Transplantation (HSCT)

Patients undergoing allogeneic HSCT tend to be heavily immunosuppressed, including immunoablative therapy applied prior to the infusion of the donor marrow. The incidence of HBR after HSCT is almost universal among HBsAg+ patients (Lalazar et al. 2007; Lau et al. 1997; Martin et al. 1995) and may be up to 50% in HBsAg–/anti-HBc+ patients (Hammond et al. 2009; Park et al. 2011; Seth et al. 2002; Vigano et al. 2011; Ramos et al. 2010; Knoll et al. 2004; Onozawa et al. 2005). Reverse HBsAg seroconversion describes the latter scenario in which a patient who initially lacked HBsAg becomes HBsAg positive. In HSCT patients, the risk of reverse seroconversion persists for many years because of the delay in reconstitution of the recipient's immune response to HBV. Reverse seroconversion may occur in patients who are initially anti-HBs positive: in studies measuring the anti-HBs titer serially, HSCT recipients gradually lost anti-HBs to become undetectable 1–3 years after transplantation. Meanwhile, HBV DNA increased, and HBsAg reappeared in the serum. In one retrospective study of HBsAg–/anti-HBc+ HSCT recipients, the cumulative probability of reverse seroconversion was 9% at the end of 1st year, which more than quadrupled to 43% at the end of 4th year (Hoofnagle 2009; Hammond et al. 2009).

**Fig. 16.2** Three important factors affecting the risk for HBR

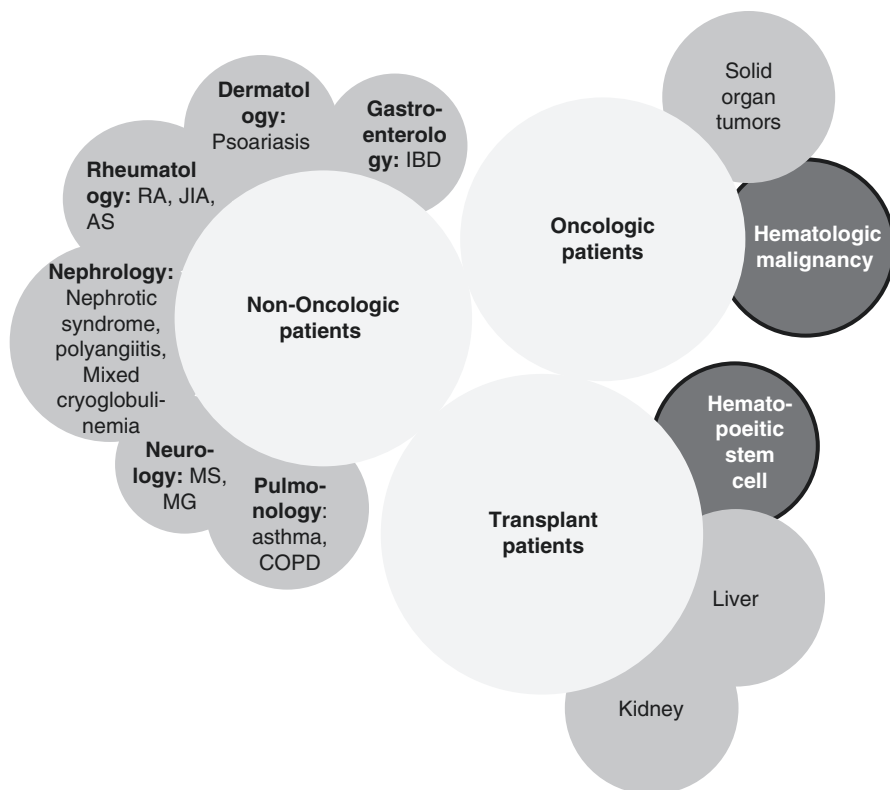


### 3.2.2 Solid Organ Transplantation (SOT)

The effect of HBV infection on the outcome of SOT has been studied most in kidney transplantation (KT). Patients with HBsAg+ have an increased risk of graft loss and mortality (Reddy et al. 2011; Fabrizi et al. 2005). The risk of HBR is higher in the HBsAg+ recipient, especially in those with detectable HBV DNA or HBeAg+ compared with HBsAg- recipients (Reddy et al. 2011). For the HBsAg+ recipients, Degos (Degos et al. 1988) demonstrated that HBR occurred in 11 of 12 (92%) initially HBsAg+ recipients. A study by Fornairon also described that 85% of HBsAg+ KT recipients developed histological progression, leading to cirrhosis and hepatocellular carcinoma in some patients (Fornairon et al. 1996). The reported HBR incidence among KT recipients with isolated anti-HBc+ was lower, varying from 0 to 6.5% (Chen et al. 2013; Kanaan et al. 2012).

## 4 Risk Assessment for HBR

The risk of HBR depends on three important factors: host, baseline status of HBV infection and the type of treatment (Fig. 16.2). Clearly, presence of HBsAg is a predominant determinant of HBR. In a study by Lau, individuals who were HBsAg+ carried a greater risk for HBV reactivation compared with those who are HBsAg- (HR 33.3, 95%CI 7.4–142.9,  $p < 0.01$ ). Among those with HBsAg+, the risk of HBR correlates with markers of viral replication status, namely, HBeAg and serum HBV DNA. In particular, HBV DNA levels exceeding  $10^5$  copies/mL were associated with the highest risk of HBR (Lau et al. 2002). Compared to undetectable HBV DNA, detectable viremia was associated with a HR of 9.35 (95%CI 1.65–52.6,  $p = 0.01$ ). Another study by Yeo evaluated risk for HBR among cancer patients treated with chemotherapy. They found that HBeAg positivity ( $p < 0.01$ ), male



**Fig. 16.3** Patients with conditions that may need immunosuppressive treatment. *IBD* inflammatory bowel disease, *RA* rheumatoid arthritis, *JIA* juvenile idiopathic arthritis, *AS* ankylosing spondylitis, *MS* multiple sclerosis, *MG* myasthenia gravis, *COPD* chronic obstructive pulmonary disease

gender ( $p = 0.045$ ), and diagnosis of lymphoma ( $p = 0.03$ ) were associated with HBR (Yeo et al. 2000a). Other studies showed that among patients with solid organ tumors, HBR occurs more commonly in breast cancer patients (41%) compared with other organs (7–29%) (Yeo et al. 2003, 2004a). The presence of anti-HBs is in general protective, depending on the host and treatment factors. The role of quantitative anti-HBs titers in the prediction of HBR in these settings is not clear.

In addition to the viral characteristics, host and treatment factors play an important role in determining the risk of HBR. Figure 16.3 shows categories of patients requiring immunosuppressive treatment. Organ transplantation carries an immense risk of HBR, especially HSCT, which affects the host immune function most profoundly. The risk of HBR in patients receiving immunosuppression in settings other than transplantation correlates with the type and level of immunosuppression. For example, the risk is highest when the regimens contain rituximab or high-dose corticosteroid (Cheng et al. 2003; Abramson and Chung 2014; Mendez-Navarro et al. 2011; Mozessohn et al. 2015; Kim et al. 2010; Yeo et al. 2009).

**Table 16.1** Risk stratification for hepatitis B reactivation (HBR) based on the types of immunosuppressive agents and HBV serologic status

Risk of HBR	HBsAg+/anti-HBc+	HBsAg-/anti-HBc+
High	<ul style="list-style-type: none"> <li>– B-cell-depleting agents, e.g. rituximab, ofatumumab</li> <li>– Anthracycline derivatives, e.g. doxorubicin, epirubicin</li> <li>– Moderate- or high-dose corticosteroids<sup>a</sup> daily for <math>\geq 4</math> weeks</li> </ul>	<ul style="list-style-type: none"> <li>– B-cell-depleting agents, e.g. rituximab, ofatumumab</li> </ul>
Moderate	<ul style="list-style-type: none"> <li>– TNF-<math>\alpha</math> inhibitors, e.g. etanercept, adalimumab, certolizumab, infliximab</li> <li>– Cytokine or integrin inhibitors, e.g. abatacept, ustekinumab, natalizumab, vedolizumab</li> <li>– Tyrosine kinase inhibitors, e.g. imatinib, nilotinib</li> <li>– Low-dose corticosteroids daily for <math>\geq 4</math> weeks</li> </ul>	<ul style="list-style-type: none"> <li>– TNF-<math>\alpha</math> inhibitors, e.g. etanercept, adalimumab, certolizumab, infliximab</li> <li>– Cytokine or integrin inhibitors, e.g. abatacept, ustekinumab, natalizumab, vedolizumab</li> <li>– Tyrosine kinase inhibitors, e.g. imatinib, nilotinib</li> <li>– Moderate- or high-dose corticosteroids daily for <math>\geq 4</math> weeks</li> <li>– Anthracycline derivatives, e.g. doxorubicin, epirubicin</li> </ul>
Low	<ul style="list-style-type: none"> <li>– Traditional immunosuppressive agents, e.g. azathioprine, 6-mercaptopurine, methotrexate</li> <li>– Intra-articular corticosteroids</li> <li>– Any dose of oral corticosteroids daily for <math>\leq 1</math> week</li> </ul>	<ul style="list-style-type: none"> <li>– Traditional immunosuppressive agents, e.g. azathioprine, 6-mercaptopurine, methotrexate</li> <li>– Low-dose corticosteroids daily for <math>\geq 4</math> weeks</li> <li>– Intra-articular corticosteroids</li> <li>– Any dose of oral corticosteroids daily for <math>\leq 1</math> week</li> </ul>

<sup>a</sup>Definitions of corticosteroid doses

High dose: >20 mg prednisone daily or equivalent

Moderate dose: 10–20 mg prednisone daily or equivalent

Low dose: <10 mg prednisone daily or equivalent

Table 16.1 categorizes the risk of HBR based on the types of immunosuppressive agents and HBV serologic status of the patients. Three strata in HBR risk may be defined, high-, intermediate-, and low-risk groups, corresponding to anticipated incidence of >10%, 1–10%, and <1% of cases, respectively. These categories inform patient management, as described later in this chapter.

## 5 Diagnosis for HBR

Uniform, standardized nomenclature and definitions for HBR are unavailable. The most recent publication aimed toward a consensus was put forth as proceedings of the 2013 Emerging Trends Conference organized by the American Association for the Study of Liver Diseases (AASLD) on the topic of reactivation of hepatitis B (American Association for the Study of Liver Diseases 2013). Table 16.2 summarizes diagnostic criteria that we propose in part based on the AASLD report.



**Table 16.2** Diagnostic criteria for HBV reactivation

Baseline status	HBsAg+	HBeAg–	HBsAg–
	HBeAg+/-		
Criteria	HBV DNA $\uparrow \geq 2$ log regardless of ALT		HBsAg+ (e seroreversion) HBsAg+ (s seroreversion)
	HBV DNA $\uparrow \geq 1$ log in association with ALT $\uparrow$		
	De novo appearance of HBV DNA $\geq 100$ IU/ml		

In patients with chronic HBV infection (HBsAg + and anti-HBc +), HBR is most commonly diagnosed by an increase in HBV DNA in the setting of immunosuppression. A consensus is lacking regarding the threshold in the rise of HBV DNA. In our view, an abrupt increase of  $\geq 2$  log in HBV DNA would be sufficient to diagnose HBR, regardless of changes in ALT. Similarly, in patients who were previously undetectable, a new appearance of HBV DNA at titers above 100 IU/ml would correspond to a 2 log rise. In patients with a clinically significant rise in ALT, a smaller degree of HBV DNA rise ( $\geq 1$  log) should trigger management actions (Di Bisceglie et al. 2015; Hwang and Lok 2014).

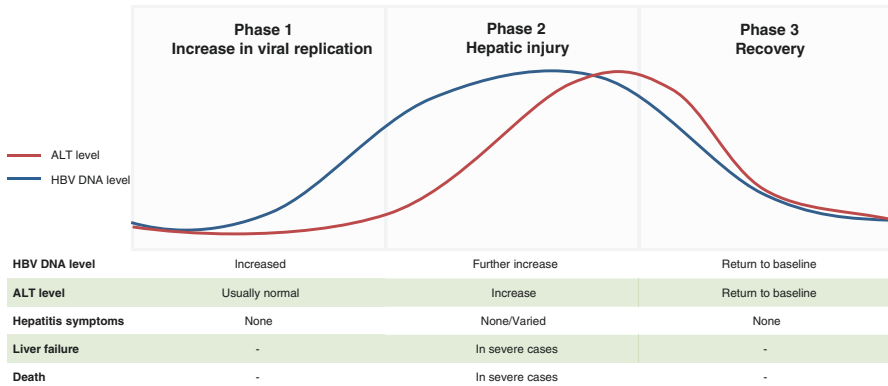
There is even less clarity regarding what degree of ALT changes is needed to define HBR. Possible proposals have included (1) multiples of the baseline ALT (e.g., threefold increase), (2) multiples of the upper limit of normal (e.g., three times the upper limit of normal), or (3) an absolute cutoff (e.g., 100 IU/mL). The difficulty is compounded by the lack of uniform definition of normal ALT values and poor standardization across laboratories for ALT assays. In our practice, a twofold increase from the patient's prior baseline is sufficient to prompt a diagnostic investigation.

Changes in the serological profile are easier to define and likely to connote more serious consequences of HBR. HBe seroreversion, namely, reappearance of HBeAg with or without the loss of anti-HBe, signals a significant shift in the immune status of the patient, corresponding to a diagnosis of HBR. HBs seroreversion is even more serious (Hwang and Lok 2014). Most patients experiencing HBs seroreversion have the baseline profile of HBsAg- and anti-HBc+; however, in patients receiving profound levels of immunosuppression (e.g., allogeneic HSCT), HBs seroreversion from anti-HBs-positive to HBsAg-positive status may occur and herald a severe degree of HBR.

## 6 Clinical Manifestations of HBR

The clinical features of HBR vary from asymptomatic changes in the laboratories to fulminant hepatic failure leading to death. The majority of patients present with mild degree of HBR.

The course of HBR has been described in three phases (Fig. 16.4). The first phase is mainly a virological event, characterized by an abrupt increase in viral replication soon after immunosuppressive therapy is initiated. There are no apparent hepatitis symptoms, and serum aminotransferase levels are usually unchanged from



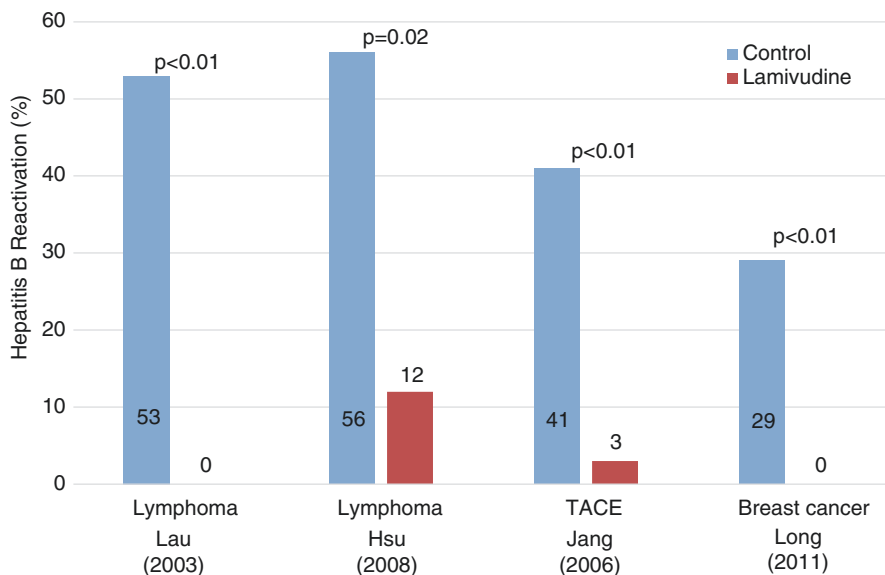
**Fig. 16.4** Phases of HBV reactivation (Reprint with permission from Hwang JP, Lok ASF. Management of patients with hepatitis B who require immunosuppressive therapy. *Nat Rev Gastroenterol Hepatol* 2013;11(4))

baseline. HBV DNA levels continue to rise during the second phase and may be accompanied by elevation in serum aminotransferases with or without symptoms such as fatigue. In severe cases, hepatitis activities may be severe enough to result in liver failure. As expected, these poor outcomes tend to occur more frequently in cirrhotic patients. In the third phase, HBV DNA levels and serum aminotransferases levels start to decrease, and HBV markers may return to the baseline. Not all HBR patients go through these three phases.

## 7 Management Strategies for Hepatitis B Reactivation

The goal in the management of HBR is two-fold: (1) prevent liver-related morbidity and mortality and (2) allow the immunosuppressive therapy to continue unperturbed. In achieving these goals, the most effective strategy is to prevent HBR to begin with. This principle is best demonstrated in randomized controlled trials that compared prophylactic antiviral therapy in patients considered to be at high risk versus withholding antiviral treatment until a diagnosis of HBR is established. Figure 16.5 summarizes the results of trials in which lamivudine was used to prevent HBR (Lau et al. 2003; Hsu et al. 2008; Jang et al. 2006; Long et al. 2011). In patients who did not receive prophylactic antivirals, HBR occurred in 30–50%—more frequently in lymphoma patients. Prophylactic lamivudine was able to virtually eliminate HBR. While lamivudine may not be the ideal agent today, these data are convincing that in high-risk patients, prevention is a preferred strategy than reactive treatment of HBR once it has occurred.

Recently, American Gastroenterological Association (AGA) released a technical review and guideline on the prevention and treatment of HBR during immunosuppressive drug therapy (Perrillo et al. 2015; Reddy et al. 2015). Table 16.3 summarizes recommendations addressed in the document.



**Fig. 16.5** Results from multiple trials showing the effect of lamivudine in the prevention of HBR (Lau et al. 2003, Hsu et al. 2008; Jang et al. 2006; Long et al. 2011)

## 7.1 Screening and Risk Stratification

A crucial element in HBR management is to identify patients with HBV infection prior to initiation of immunosuppressive therapy. Various governmental and professional organizations have published guidelines about screening as shown in Table 16.4 (Reddy et al. 2015; Weinbaum et al. 2008; Lok and McMahon 2009; Baden et al. 2012; European Association for the Study of the Liver 2012; LeFevre 2014; Sarin et al. 2016; Hwang et al. 2015). Although these guidelines vary in some of the details in their recommendations, they all agree that initial screening should be performed with HBsAg and anti-HBc. Regarding anti-HBc testing, it can be either total anti-HBc or anti-HBc immunoglobulin G, but not immunoglobulin M.

An approach to diagnose all patients at risk of HBR would be universal screening—namely testing every patient for HBV infection before immunosuppressant therapy is instituted. For example, the US Food and Drug Administration (FDA) recommends all healthcare providers to routinely screen all patients for HBV infection prior to the initiation of chemotherapy or immunosuppressive therapy. A study by Hwang found that case identification was substantially improved through universal screening rather compared to the usual practice (Hwang et al. 2012). While it would detect the most number of patients with HBV infection and optimize patient management, this approach is not widely practiced because most oncologists do not perceive the benefit of universal screening to be large enough to justify the efforts and expenses needed, particularly in low HBV prevalence settings such as the US general practice. Presumably, if HBV prevalence is high enough, universal

**Table 16.3** AGA recommendations on the prevention and treatment of HBR in patients undergoing immunosuppressive therapy (Reddy et al. 2015)

Questions	Recommendations	Levels of recommendations
Screening and risk stratification		
• Should patients who will undergo long-term immunosuppressive drug therapy be screened for HBV before starting treatment?	High and moderate risk: Screen with HBsAg and anti-HBc, followed by a sensitive HBV DNA test if positive	Strong recommendation; moderate-quality evidence
	Low risk: No screening	Weak recommendation; moderate-quality evidence
• Does the presence of HBsAb in HBsAg–/HBcAb+ patients confer additional protection against HBR?	Anti-HBs status not to be used to guide antiviral prophylaxis for all risk groups	Weak recommendation; very-low-quality evidence
Antiviral prophylaxis		
• Is antiviral prophylaxis needed for HBsAg+ patients undergoing immunosuppressive drug therapy?	High risk: Recommend antiviral prophylaxis	Strong recommendation, moderate-quality evidence
	Moderate risk: Recommend antiviral prophylaxis	Weak recommendation; moderate-quality evidence
• Is antiviral prophylaxis needed for HBsAg–/HBcAb+ patients undergoing immunosuppressive drug therapy?	Low risk: Not recommend routinely using antiviral prophylaxis	Weak recommendation; moderate-quality evidence
• Is prophylactic treatment with third-generation nucleos(t)ide analogues (NAs) more effective than first- or second-generation NAs?	Use antiviral drugs with a high barrier to resistance over lamivudine for prophylaxis	Weak recommendation; moderate-quality evidence
Rescue therapy for established HBR		
• Is HBV DNA monitoring followed by on-demand antiviral therapy as effective as prophylactic antiviral therapy?	No recommendation for a strategy of HBV DNA monitoring followed by rescue treatment as an alternative to antiviral prophylaxis	No recommendation—knowledge gap
• Is treatment of established HBR with third-generation NAs more effective than first- or second-generation drugs?	Use antiviral drugs with a high barrier to resistance over lamivudine	Strong recommendation; moderate-quality evidence

screening may prove to be cost-effective. To date, available cost-effectiveness analyses suggested that universal screening with HBsAg and anti-HBc is not cost-effective in palliative or adjuvant setting for solid tumors but it is cost-saving for lymphoma patients undergoing chemotherapy with a rituximab-containing regimen (Day et al. 2011; Zurawska et al. 2012).

An alternate strategy in screening for HBR prophylaxis candidates is to stratify individual patients according to their risk of HBR. The recommendations by AGA in Table 16.3 utilize such a risk stratification scheme. Based on the immunosuppressive regimen and the serologic profile (see Table 16.1), the patient may be classified as

**Table 16.4** Recommendation for HBV screening in order to prevent HBR from various organizations

Organizations	Population to be screened	Screening tests	References
CDC <sup>a</sup> (2008)	All patients before immunosuppression	HBsAg, anti-HBc, anti-HBs	Weinbaum et al. (2008)
AASLD <sup>b</sup> (2009)	All patients with high risk for HBV infection	HBsAg, anti-HBc	Lok and McMahon (2009)
NCCN <sup>c</sup> (2012)	All patients with B-cell lymphoid malignancies, high risk for HBV infection, intensive immunosuppression especially anti-CD20 monoclonal antibody	HBsAg, anti-HBc, anti-HBs	Baden et al. (2012)
EASL <sup>d</sup> (2012)	All patients before immunosuppression	HBsAg, anti-HBc	European Association for the Study of the Liver (2012)
USPSTF <sup>e</sup> (2014)	All patients with high risk for HBV infection	HBsAg, anti-HBc, anti-HBs	LeFevre (2014)
APASL <sup>f</sup> (2015)	All patients before immunosuppression	HBsAg; anti-HBc if needs anti-CD20 monoclonal antibody or anti-TNF	Sarin et al. (2016)
AGA <sup>g</sup> (2015)	All patients before immunosuppressive therapy at moderate/high risk of HBV reactivation, but not before low-risk therapy	HBsAg, anti-HBc	Reddy et al. (2015)
ASCO <sup>h</sup> (2015)	All patients with high risk for HBV infection and before starting anti-CD20 therapy or hematopoietic cell transplantation	HBsAg, anti-HBc	Hwang et al. (2015)

<sup>a</sup>CDC = Centers for Disease Control and Prevention

<sup>b</sup>AASLD = American Association for the Study of Liver Diseases

<sup>c</sup>NCCN = National Comprehensive Cancer Network

<sup>d</sup>EASL = European Association for the Study of the Liver

<sup>e</sup>USPSTF = US Preventive Services Task Force

<sup>f</sup>APASL = Asian Pacific Association for the Study of the Liver

<sup>g</sup>AGA = American Gastroenterological Association

<sup>h</sup>ASCO = American Society of Clinical Oncology

high, moderate, and low risk. High- and moderate-risk patients should receive HBV screening, whereas screening may be reserved for certain low-risk patients who meet the screening criteria recommended for the general population according to the CDC and the US Preventive Service Task Force. Patients are screened for HBsAg and anti-HBc, followed by HBV DNA, if either is positive. The advantage of this risk stratification strategy is that it is more likely to be cost-effective than universal screening and reduce the potential harm of false-positive results. However, it is limited by the complexity in its application. In clinical scenarios where care is being planned for a

cancer patient requiring chemotherapy or a patient with an immunological disorder in need of immunosuppressive therapy, applying the HBR risk rules may not be considered high priority, and screening may not be performed at all.

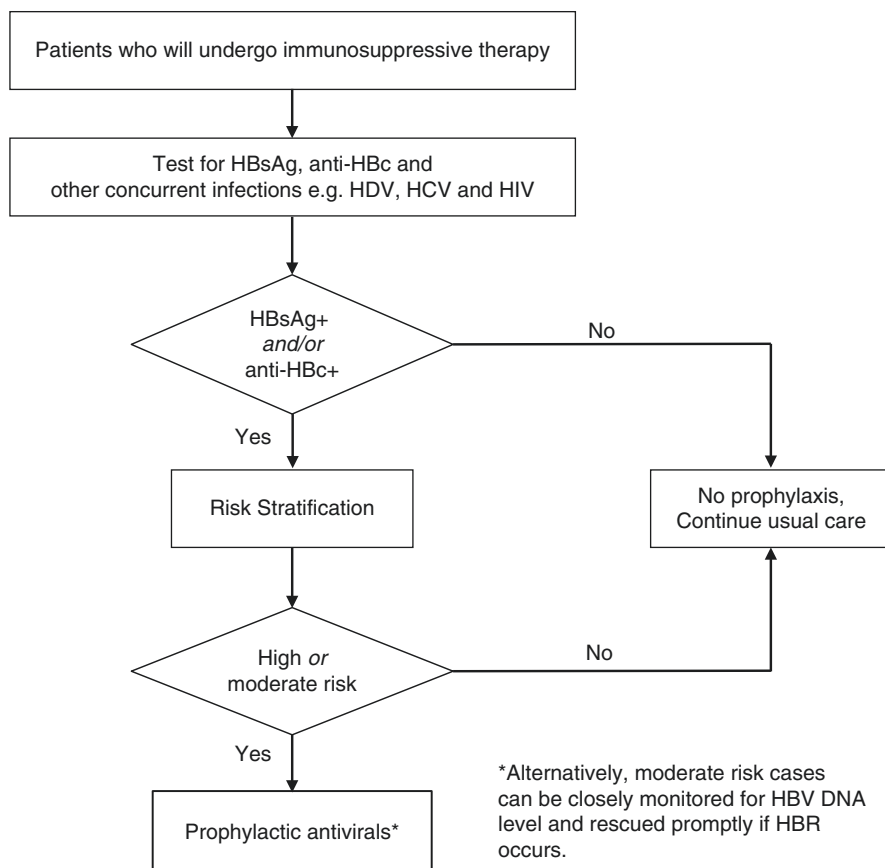
Finally, the guideline addresses the utility of anti-HBs in the management of HBR. It is often believed that the presence of anti-HBs makes it less likely that the patient will experience HBR. However, HBR may occur despite anti-HBs, particularly in patients undergoing the deepest level of immunosuppression (e.g., HSCT), in whom HBR may occur in conjunction with HBs seroreversion. The guideline recommends against using anti-HBs status in determining the need for antiviral prophylaxis regardless of the risk level.

## 7.2 Antiviral Prophylaxis Algorithm

The next set of questions in the management of patients at risk of HBR addresses (1) who are candidates for antiviral prophylaxis and (2) what antiviral regimen should be used. Figure 16.6 represents an algorithm that we propose, based on the AGA guideline for the management of patients undergoing immunosuppressive therapy to optimize their outcomes with regard to HBR. Once a decision is made how screening is performed (universal versus risk-stratified), the patient will undergo testing for a minimum of HBsAg and anti-HBc. Depending on the patient's risk profile, additional testing for hepatitis C, human immunodeficiency virus or hepatitis D (if HBsAg is positive) may also be considered.

In a patient who is negative for both HBsAg and anti-HBc, there is no need for antiviral prophylaxis. If, however, the patient is either HBsAg+ or anti-HBc+, the risk of HBR needs to be assessed. If the patient meets the high-risk criteria (Table 16.1), prophylactic antiviral is indicated, whereas in a patient who is at low risk, prophylaxis is not recommended. In patients who are at moderate risk, the guideline expresses preference for antiviral prophylaxis. However, the evidence to support the recommendation is not very robust, and an alternate approach may be to monitor HBV DNA levels for early detection and prompt treatment for HBR. However, there is no consensus about optimal ways to monitor for HBR both during and after cessation of immunosuppressive therapy, although some have suggested a monitoring interval of 3 months (Hwang and Lok 2014). In our opinion, upfront institution of antiviral prophylaxis obviates the cost and inconvenience of repeated HBV DNA testing, especially if the antiviral therapy can be delivered inexpensively. We do concur with the AGA guideline which recommended that in patients who place a higher value on avoiding any long-term use of antiviral therapy and costs associated with its use and consider avoiding the small risk of reactivation less important, it may be reasonable to choose no prophylaxis over antiviral prophylaxis, particularly if HBsAg is negative.

With regard to the choice of prophylactic antiviral agent, lamivudine has been most widely studied (Yeo et al. 2004b, c; Lau et al. 2003; Hsu et al. 2008; Jang et al.



**Fig. 16.6** Algorithm for HBV screening and antiviral prophylaxis to prevent HBR in non-transplant patients

2006; Loomba et al. 2008; Ahmed and Keeffe 1999; Kohrt et al. 2006; Li et al. 2006; Rossi et al. 2001; Nagamatsu et al. 2004; Dai et al. 2004). Those studies showed that lamivudine improved outcome of patients with respect to HBR, including the occurrence of HBR, the need to delay or interrupt chemotherapy, and ultimately the outcome of the cancer therapy. While lamivudine was effective in proving the concept of antiviral prophylaxis of HBR, it has fallen out of favor in the treatment of chronic HBV infection in general, due in part to its susceptibility to viral mutations that negate its efficacy and lower potency compared to more modern agents. The AGA guideline prefers a third-generation NA over lamivudine for HBR prophylaxis. A randomized controlled trial showed the superiority of entecavir over lamivudine in decreasing the risk of HBR, hepatitis B flare, and interruption of

immunosuppressive therapy (Huang et al. 2013). There are other studies with a similar conclusion, although the quality of those studies is not as robust.

A counterargument in favor of lamivudine is that most patients receiving antiviral prophylaxis have low or undetectable levels of HBV DNA at baseline and lamivudine failure is expected to be infrequent. The AGA guideline acknowledges this trade-off: it suggests that in patients who put a higher value on cost of antiviral therapy and a lower value on avoiding the potentially small risk of resistance development, it may be reasonable to select the least expensive anti-HBV medication over more expensive antiviral drugs with a higher barrier to resistance. In patients with undetectable viral load with expected duration of prophylaxis for 6 months or less, lamivudine may be acceptable.

Data are sparse as to the optimal timing of the initiation and discontinuation of antiviral prophylaxis. In our practice, we try to start HBR prophylaxis as soon as the need is determined. For patients with low or undetectable viremia, prophylaxis initiation concurrent to immunosuppressive therapy would be sufficient. In patients with higher levels of HBV DNA, we expect it to be advantageous if HBR prophylaxis can precede the onset of immunosuppression. However, immunosuppressive therapy, especially cancer chemotherapy, should not be delayed on account of achieving viral suppression. With regard to the duration of therapy, the AGA guideline recommends the prophylaxis to continue for at least 6 months after discontinuation of immunosuppressive therapy, with the exception of patients receiving B-cell-depleting agents, in whom prophylaxis is extended to 12 months.

### 7.3 Treatment of Established HBR

Any abnormalities in liver test of patients undergoing immunosuppressive therapy or chemotherapy need to be carefully investigated. It is necessary to differentiate HBR from various potential causes including infections from other hepatitis virus (A, C, D, and E), opportunistic pathogens (e.g., cytomegalovirus), drug-induced liver injury, or other causes (e.g., graft-versus-host disease). In patients who have been screened for HBV infection and deemed to be at moderate risk for HBR and elect to be monitored without prophylactic antiviral therapy, HBR may be diagnosed early by rising HBV DNA levels before biochemical or clinical evidence of hepatitis activities emerges. Whether employing the so-called on-demand rescue therapy in that setting is inferior to upfront prophylaxis remains uncertain, and the AGA guideline makes no recommendation about such a strategy. In patients who were not screened initially and develop active hepatitis B, HBR may be misdiagnosed as acute HBV infection since anti-HBc IgM may be detected in severe hepatitis B flare (Law et al. 2016).

Once the diagnosis of HBR is established, the treatment goal is to prevent severe hepatitis and hepatic failure. This may be achieved by (1) effective and expeditious viral control and (2) monitoring and supportive treatment for hepatic insufficiency. To achieve viral control, potent oral NAs must be initiated as soon as possible, although high-quality evidence demonstrating the efficacy of antiviral therapy in



reducing morbidity and mortality in patients with HBR is lacking (Liao et al. 2002). Delay in institution of antiviral therapy may lead to hepatic failure, liver transplantation, and death, and interferon-based therapy is inappropriate in this setting (Lok et al. 1991; Lau et al. 2003; Jindal et al. 2013; Hsu et al. 2014).

With regard to the choice of antiviral agents, there have been no randomized studies of the clinical effectiveness comparing third-generation NAs with earlier generation agents. In part based on data in immunocompetent patients, the AGA guideline recommends entecavir or tenofovir in this setting (Perrillo et al. 2015). There are little data to define the optimal duration of therapy—it may take patients with established HBR longer to bring HBV replication under control compared to patients with low viral burden undergoing antiviral prophylaxis (Hwang and Lok 2014). In patients with satisfactory viral control, we believe it would be reasonable to apply the same rule for therapy discontinuation as that for prophylaxis. In most patients, antiviral therapy should be continued for at least 6 months after discontinuation of immunosuppressive therapy. In population treated with a B-cell-depleting regimen, consideration should be given to continue the therapy for at least 12 months after discontinuation of immunosuppressant.

In patients whose HBR progresses to symptomatic hepatitis and develop signs of hepatic insufficiency, rapid cessation of ongoing necro-inflammation and loss of functioning hepatocyte mass is even more important. While the definitive treatment for liver failure would be liver transplantation, rarely patients with HBR are candidates for liver transplantation because of their underlying disease (Noterdaeme et al. 2011). However, we believe that these patients should be cared for by a team of healthcare providers with hepatology expertise to maximize support and afford a chance for recovery.

## 7.4 Management of Transplant Recipients

In addition to being subjected to immunosuppression, organ transplant recipients may develop HBR as a result of transmission of donor-derived HBV. The risk of HBV transmission is highest in liver transplantation, since hepatocytes are the primary site of HBV infection. However, recipients of other organs may also be at risk for HBV infection. Several management guidelines have been published in order to enhance the quality of care and improve the efficiency of HBR prevention in transplanted patients (Tomblin et al. 2009; Kasiske et al. 2010). Care of liver transplantation patients is discussed elsewhere.

In general, both donors and recipients should be tested for HBsAg, anti-HBs, and anti-HBc. If the recipient is either HBsAg+ or anti-HBc+, he/she should be tested for HBV DNA. Non-HSCT candidates who are HBsAg+ or HBV DNA+ should receive antiviral prophylaxis. Whenever possible, HBsAg- candidates should be immunized against HBV and the response to vaccination be confirmed. Transplant recipients who are HBsAg-/anti-HBc+ may be managed in a similar fashion as immunosuppressed patients at moderate risk—they may be given antiviral prophylaxis or monitored for HBV DNA level for early detection of HBR followed by

preemptive treatment. All candidates with evidence of active HBV DNA replication (either HBsAg+ or detectable HBV DNA) should be evaluated for the degree of liver fibrosis, preferably by a liver biopsy, prior to the transplantation, since advanced fibrosis/cirrhosis can increase treatment-related morbidity and mortality.

A special consideration is given for HSCT patients. HSCT candidates should be immunized prior to chemotherapy with the initial two doses given 3–4 weeks apart, followed by the third dose 6 months later. If this schedule cannot be met, the third dose may be administered a few months after completion of chemotherapy. If anti-HBs titer after vaccination is <10 IU/L or pre-transplant vaccination is impractical, hepatitis B immune globulins (HBIG) at a dose of 0.06 ml/kg should be administered immediately prior to infusion of stem cells.

HSCT donors with detectable HBV DNA should be treated with antivirals for at least 4 weeks or until HBV DNA becomes undetectable. The cell volume from HBsAg+ and/or anti-HBc+ should be minimized and all cell products be tested for HBV DNA at the time of harvest. If HBV DNA is detectable at harvest either in the donor or harvested cells, the recipients should receive antiviral prophylaxis and optionally HBIG for 4 weeks after transplantation. If HBV is undetectable in the donor and harvested cells, recipients may be monitored with monthly ALT for the first 6 months. If ALT increases, HBV DNA and HBsAg should be tested. If there is detectable HBV DNA or HBsAg+, preemptive therapy is needed (Tomblyn et al. 2009).

With regard to kidney transplantation, a kidney from an HBsAg+ donor should not be transplanted into an HBsAg- recipient as there is a significantly high risk for HBV transmission. A kidney transplant from a donor with isolated anti-HBc+ possesses a relatively low risk of transmission and may be considered for candidates with anti-HBs+ (Abrao et al. 2014).

According to the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline on the monitoring, management, and treatment of kidney transplant recipients, if KT candidates have postvaccination anti-HBs titer <10 IU/L, booster vaccination should be administered in an attempt to raise the titer to  $\geq 100$  IU/L. In those with ongoing HBV infection, adequate suppression of HBV must precede the transplant. Prior to the availability of oral antiviral agents, recipients with HBsAg+ had 2.5-fold increased risk of death and 1.4-fold increased risk of allograft loss compared to HBsAg- recipients (Fabrizi et al. 2005). More recent data in the era of oral antiviral agents indicate improved survival of KT recipients with HBV infection. Five-year survival rates of KT recipients with and without HBV infection were 85% versus 86%, respectively. Graft survival was also similar approximately at 75% (Reddy et al. 2011). These support KDIGO recommendations that recipients with HBsAg+ must be given antiviral therapy. For recipients with isolated anti-HBc+, there is insufficient evidence to recommend routine antiviral prophylaxis. However, we suggest to follow AGA guideline to judge the need for prophylactic treatment. Regarding the choice of antivirals, entecavir is a preferable choice for KT recipients due to its high barrier of resistance and non-nephrotoxic property. Interferon should be avoided as it is associated with the increased risk of acute rejection (Kasiske et al. 2010).

HBsAg-positive KTx recipients receiving prophylaxis must be monitored closely, although the optimal monitoring strategy to detect HBR remains to be

defined. For patient with high viral load prior to the prophylactic treatment, HBV DNA may be checked every 1–3 months until it becomes undetectable before initiation of immunosuppression. During the period of immunosuppression, HBV DNA should be checked every 3–6 months to ensure viral suppression. For those who are not on prophylactic antiviral therapy, ALT may be checked every other week for the first 16 weeks then every 3–4 weeks for the first years. HBV DNA should be monitored every month for the first year. If there is an increase in ALT level, evaluation of HBR should be performed, and preemptive therapy is needed when HBR is established (Chan and Lok 2016).

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## 8 Emerging Trend: HBV Reactivation After Successful Treatment of Hepatitis C

HBV/HCV dual infection is not uncommon especially in the endemic areas of HBV and among high-risk population as these two viruses share similar routes of transmission. The prevalence of dual infection with HBV has been reported from 5% to 20% of individuals with HCV infection (Chu and Lee 2008). In addition, occult HBV infection, defined by the presence of HBV DNA in the absence of HBsAg, may be found in 12–44% of HCV-infected patients (Fukuda et al. 1999). As commonly seen in patients with infection with multiple hepatotropic viruses, in HBV/HCV dual infection, one of the viruses predominates (as measured by the viral load), which tends to be HCV.

Direct-acting antivirals against HCV available today afford high rates of cure. Recently, the US FDA has warned of the risk of HBR in patients with HBV/HCV dual infection treated with DAAs. Although HBR has been previously reported with interferon and ribavirin, HBR may occur much more rapidly during DAA treatment. The mechanism behind HBR after DAA therapy remains unclear. In experimental conditions, HBV and HCV could replicate in the same hepatocyte without evidence of interference, suggesting that HCV may suppress HBV replication via an indirect mechanism (Yang et al. 2014)—relatively abrupt elimination of HCV from hepatocytes would disinhibit HBV replication. It has also been postulated that the clearance of HCV may mitigate the immune control (e.g., downregulation of previously overexpressed IFN-stimulated genes).

To date, there have been 24 cases with HBR identified in the FDA Adverse Event Reporting System (FAERS) database and/or reported in the published medical literature. HBR has been reported in various DAA regimens including simeprevir and sofosbuvir (Collins et al. 2015), daclatasvir and asunaprevir (Hayashi et al. 2016; Takayama et al. 2016), and ledipasvir and sofosbuvir (De Monte et al. 2016). As expected, HBR has been reported more commonly in patients with HBsAg-positive dual infection compared to those with isolated anti-HBc positivity. In an observational study in Chinese patients treated with DAAs, 3/10 HBsAg+ patients developed HBR, compared to none of 124 who were HBsAg negative and anti-HBc positive. In most cases, HBR occurred within 4–8 weeks after starting DAA therapy. These patients were heterogeneous in terms of HCV genotype and baseline HBV

**Table 16.5** Approach to prevent HBR in patients with dual HBV/HCV infection

Goal	Candidate	Action
Screen	All HCV patients being considered for DAA therapy	HBsAg, anti-HBc, and anti-HBs
	If HBsAg or anti-HBc-positive	HBV DNA
Prophylaxis	HBsAg positive and/or detectable HBV DNA	Assess fibrosis and determine HBV therapy candidacy and endpoints Anti-HBV therapy concurrent to DAA
	Isolated anti-HBc and undetectable HBV DNA	Monitor HBV DNA at week 4 of DAA therapy; anti-HBV prophylaxis if increasing
	Anti-HBs positive	No action
Prevention	Anti-HBs negative	Vaccinate

status. The severity of HBR in those patients varied from no symptoms to severe hepatic failure or death (U.S. Food and Drug Administration 2016).

There is insufficient data based on which to incorporate HBV/HCV dual infection patients into our management algorithm (Fig. 16.6). Table 16.5 describes our proposed approach to these patients. Patients undergoing DAA therapy must be screened for HBsAg, anti-HBc, and anti-HBs, followed by HBV DNA in patients who are either HBsAg negative or anti-HBc positive. We propose that anti-HBV prophylaxis be started concurrent with the DAA therapy in patients who are HBsAg positive or HBV DNA detectable, whereas in patients who are anti-HBc positive and HBV DNA undetectable, prophylaxis may not be necessary. In the former category of patients, it is important to determine whether the patient would have been a candidate for HBV therapy regardless of the HCV dual infection and define the HBV treatment endpoint, such as HBe seroconversion. We believe it is also important to assess their liver fibrosis status, which is commonly performed in preparation of the HCV therapy. For patients with isolated anti-HBc without detectable HBV DNA, monitoring for a rise in HBV DNA may be reasonable, perhaps at week 4 of therapy, as patients are often tested for HCV RNA at the same time.

There is no data available to inform the optimal duration of HBV therapy in dual infection patients being treated for HCV. To the degree that there may be host immunological shift that underlie the development of HBR, in our practice, we continue the prophylaxis for 3 months after discontinuation of DAA. These patients are monitored for another 3 months to ensure absence of HBR off anti-HBV prophylaxis. Obviously, in patients determined to be candidates for HBV therapy independent of HCV, therapy should be continued until the planned endpoint is met. Care must be taken in discontinuing anti-HBV prophylaxis in patients with cirrhosis, which may precipitate hepatic decompensation.

## 9 Current Challenges and Future Directions

HBR leading to a poor patient outcome such as liver failure or disruption of cancer chemotherapy represents an unnecessary clinical tragedy, which is eminently preventable by appropriate screening and prophylaxis. Despite a multitude of guidelines to inform clinicians caring for patients undergoing cancer

treatment, transplantation, and immunomodulatory therapy, HBR continues to occur (Patel et al. 2016; Yuen 2016). Survey studies conducted in practicing physicians indicate that adherence to routine HBV screening prior to the immunosuppressive therapy is unacceptably low—approximately 20–40% of oncologists, 40% of dermatologists, and 70% of rheumatologists follow a guideline in some fashion (Hwang et al. 2012; Stine et al. 2011, 2010; Tran et al. 2010; Kawsar et al. 2012).

This problem may be partly attributable to the inconsistency among the guidelines. Clearly, multi-society collaboration to develop a broadly applicable consensus is an essential step. Secondly, efforts to disseminate the consensus guideline to all practitioners are needed. For healthcare providers that are not routinely involved in the care of patients at risk of HBR, electronic mechanisms may be helpful to alert them of candidates for screening and to guide them to initiate appropriate prophylaxis. Such a proactive measure may be even more important in the future, as increasingly more complex and potent immunosuppressive and chemotherapeutic regimens are being developed.

Finally, as investigators strive toward gaining more biological insight and immunopathogenetical knowledge of HBV infection, deeper understanding of the basic mechanisms of HBV reactivation may help better inform clinical decisions for HBR. This is particularly true of the HBV/HCV dual infection cases. In addition, the effect of new therapeutic agents that interact with the immune system in a non-conventional manner on the occurrence and course of HBR remains to be studied. Finally, as new diagnostic biomarkers and therapeutic agents are being actively developed for the goal of “cure” of HBV, additional tools may become available to provide more accurate risk stratification and then inactivate, if not cure, HBV in a sustainable fashion in patients undergoing increasingly sophisticated regimens that have a diverse effect on the immune system.

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